Stem Cell-mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials

Grant Award Details

Stem Cell-mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials

Grant Type: Disease Team Research I

Grant Number: DR1-01421

Project Objective: To develop a combination cell/small molecule therapy for recurrent glioblastoma and file an IND for a Phase 1 first-in-human trial. In the Phase 1 trial, gene-modified NSCs will be injected into the resected tumor bed to track residual tumors and locally convert systemically administered CPT-11 to SN-38. Some patients will receive iron-labeled NSCs to allow cell tracking by MRI.

Investigator:

Name: Karen Aboody

Institution: City of Hope, Beckman Research Institute

Type: PI

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Name: Jana Portnow

Institution: City of Hope, Beckman Research Institute

Type: Co-PI

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Name: Larry Couture

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Type: Co-PI

Disease Focus: Brain Cancer, Cancer, Solid Tumors

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $17,890,623

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5/NCE

View Report

Grant Application Details

Application Title: Stem Cell-mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials

Public Abstract:

Despite aggressive multimodal therapy and advances in imaging, surgical and radiation techniques, malignant brain tumors (high-grade gliomas) remain incurable, with survival often measured in months. Treatment failure is largely attributable to the diffuse and invasive nature of these brain tumor cells, ineffective delivery of chemotherapeutic agents to tumor sites, and toxic side-effects to the body, which limits the dose of drug that can be given. Therefore, new tumor-selective therapies are critically needed. Neural stem cells (NSCs) offer an unprecedented advantage over conventional treatment approaches because of their unique ability to target tumor cells throughout the brain. This ability allows NSCs to be used to deliver prodrug-activating enzymes to tumors, where these enzymes will generate high concentrations of powerful anti-cancer agents selectively at tumor sites.

We will use an established human NSC line to develop a novel NSC-based product to deliver the enzyme carboxylesterase (CE), which will activate a systemically administered prodrug, CPT-11, to a powerful chemotherapeutic agent, SN-38, selectively at tumor sites, destroying invasive glioma cells while sparing normal tissues. Based on our preliminary data, we hypothesize that CE-expressing NSCs will home to tumor sites in the brain, and, in combination with CPT-11, will generate high concentrations of SN-38 specifically at tumor sites. Thus, in addition to potentially improving lifespan by concentrating the powerful chemotherapeutic agent selectively at tumor sites, this NSC-mediated treatment strategy should significantly decrease toxic side-effects to normal tissues, thus preserving or improving the patient's quality of life.

Our research, regulatory and clinical teams have the collective expertise and experience to conduct the preclinical studies necessary to optimize the efficacy of this innovative treatment approach. Specifically, we will determine the optimal dose and route of NSC administration; the optimal prodrug dosing regimen; and assess the safety of this treatment approach. We will perform these studies and analyses, generate clinical grade products, and file and obtain all appropriate regulatory documents and approvals. Completion of these activities will lead to the filing of a new Investigational New Drug (IND) proposal to the FDA, for a first-in-human Phase I clinical trial of this pioneering NSC-mediated treatment in patients with recurrent high-grade gliomas.

Importantly, our NSC line can be further modified for tumor-localized delivery of a variety of therapeutic agents, and can be given serially or in combination to maximize therapeutic benefit. Thus, the potential medical impact of this innovative NSC-mediated therapeutic approach may be very far-reaching, as it can be developed for application to other types of malignant brain tumors, as well as for metastatic cancers.

Statement of Benefit to California:

Despite aggressive multimodality therapy and advances in imaging, surgical and radiation techniques, high-grade gliomas remain incurable, with survival often measured in months. Approximately, 22,500 malignant brain tumors are diagnosed annually in the U.S., of which more than 2,600 cases are in California. New therapies are desperately needed to improve both the survival and quality of life of these brain tumor patients and to reduce the economic impact of billions of dollars in related healthcare costs.

We propose to develop a novel neural stem cell (NSC)-based treatment method that will selectively target glioma cells with a potent chemotherapy agent, locally activated by the NSCs at tumor sites to destroy neighboring tumor cells. Our tumor-selective approach also has the advantage of minimizing toxicity to normal tissues, thereby decreasing systemic side effects and damage to normal brain. This new therapeutic strategy, therefore, not only has the potential to improve survival, but, by preserving cognitive function and quality of life, it could also enable adult Californians diagnosed with brain tumors to continue making societal contributions that would benefit all Californians.

Important for clinical translation of this novel therapeutic approach, we have established the NSC line to be used in this study as a fully characterized cGMP Master Cell Bank. The NSC line is thus expandable, easily distributed to other medical centers, and cost-effective, which will allow this therapeutic approach to be quickly adopted. Importantly, this NSC line can be further modified for tumor-localized delivery of a variety of therapeutic agents, which may be given serially or in combination to maximize therapeutic benefit. There is tremendous potential for developing NSC-mediated treatment applications for other types of malignant brain tumors, as well as for metastatic solid tumors throughout the body. Therefore, the impact of these proposed studies to advance NSC-mediated treatment of glioma may be very far-reaching and may significantly contribute to reducing healthcare costs.

Finally, the combined strengths and experience of our research team will enable us to advance this NSC-meditated therapeutic approach in a timely, streamlined, and cost-effective manner to submit a new IND application for initiating first-in-human clinical trials in California, providing benefit to state taxpayers by efficient use of tax dollars and initial access to this novel therapy. In addition, our CIRM Disease Team NSC-mediated cancer treatment studies would stimulate and advance collaborative partnerships and alliances with other cancer centers and affiliates, pharmaceutical companies, academic institutions, and philanthropic societies within California, which would further enhance local and state economies.
